REMARKS/ARGUMENTS

The Pending Claims

Claims 5, 8, 10-12, 18, 20, and 32-35 are pending and are directed to a method of enhancing an immune response in a subject (claims 5, 8, 10-12, 32, and 34) and a method of treating a subject with a condition comprising a deficiency of at least one of memory B cells and plasma cells (claims 18, 20, 33, and 35).

Amendments to the Claims

Claims, 1, 18, 34, and 35 have been amended to recite variants of the IL-21 polypeptide as supported by the specification at, for example, page 31, lines 1-27.

The second set of claims inadvertently numbered as 32 and 33 have been renumbered as claims 34 and 35, respectively, in accordance with the requirement in the Office Action dated April 29, 2008.

No new matter has been added by way of these amendments to the claims. Entry of the above is hereby requested.

Summary of the Office Action

The Office objects to the specification because a statement that the information recorded in computer readable form is identical to the written sequence listing is required.

The Office rejects claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description.

The Office rejects claims 5, 8, 10-12, 18, 20, and 32-35 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement.

The Office objects to misnumbered claims 32 and 33 for having incorrect (duplicate) claim numbers.

Reconsideration of these objections and rejections is hereby requested.

Examiner Interview

Applicants thank Examiner Leavitt for the courtesies extended to Applicants' representative Rachel J. Mejdrich during the telephone interview of June 16, 2008. During the interview, Examiner Leavitt clarified the objection to the specification.

Discussion of the Objection to the Specification

The Office requires a statement that the information recorded in computer readable form is identical to the written sequence listing. Applicants note that only a computer-readable form of the replacement sequence listing (and not a written sequence listing) was submitted electronically with the Reply to Office Action dated January 17, 2008.

The computer readable form of the replacement sequence listing is identical to the originally filed sequence listing (submitted in written form), except that the replacement sequence listing contains SEQ ID NO: 17. The originally filed specification contains the sequence corresponding to SEQ ID NO: 17 (WSXWS; see, page 19, line 20). Therefore, no new matter was added by way of the entry of the replacement sequence listing into the specification.

Applicants request that the objection to the specification be withdrawn.

Discussion of the Written Description Rejection

The Office contends that the specification does not provide adequate written description for the genus of IL-21 agonists and variants that differ from SEQ ID NO: 1 by 1-5 amino acids. The Office contends that the specification only mentions the full length IL-21 of SEQ ID NO: 1, and that the specification does not disclose regions or domains of the protein that are essential to bind the IL-21 receptor resulting in the claimed physiological effects. In particular, the Office contends that the specification does not disclose what amino acids are in the active site, the binding pocket, or the hydrophobic core of the protein.

The pending claims, as amended, recite an IL-21 polypeptide comprising SEQ ID NO: 1 or a variant thereof that retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor. The specification describes

variants for use in the invention at, for example, page 31, lines 1-26. In particular, the specification cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retaining the essential properties thereof. In particular, Ebner et al. discloses conserved regions of IL-21 polypeptide in Figures 1, 4, 6A-B, and 7, and Tables I-III. Furthermore, Ebner et al. discloses regions of identity between IL-21 and other interleukins in Figures 3A-C. Thus, regions of IL-21 polypeptide that should not be mutated were known in the art. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

Furthermore, as discussed previously, assays to determine suitable variants are described in the specification or known in the art. For example, the claims require that the IL-21 variant produces the same physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20), induces expression of mRNA for Blimp-1 and Bcl-6 (see, e.g., page 53, lines 27-29), and inhibits expression of Pax5 mRNA (see, e.g., page 53, lines 27-30). Assays to determine if an IL-21 variant produces the above-described effects (e.g., real-time PCR) are known in the art and are described in the specification at, for instance, page 41, line 19, through page 44, line 16; and Examples 3-5.

Accordingly, based on the teachings in the specification and what was known in the art, one of ordinary skill in the art would have recognized that Applicants had possession of an IL-21 polypeptide variant for use in the inventive methods.

Discussion of the Enablement Rejection

The Office contends that the specification is not enabling for *ex vivo* methods of therapy. In particular, the Office contends that the claims encompass a method of inducing an immune response against a viral infection; however, the Office contends that it is unclear how an immune response against a viral infection is effective merely by a humoral response (e.g., a memory B cell and a plasma cell) as viruses are intracellular pathogens and an effective response against intracellular viral pathogens requires cell-mediated immunity

(processing and association of the viral antigen with the MHC Class I molecule on APC cell surface for activation of T cells) (see, page 9, last paragraph, of the Office Action dated April 29, 2008).

Applicants note that claims 5, 7, 10-12, 32, and 33 are directed to a method of *enhancing* an immune response by administering one or more of a memory B cell and the plasma cell produced *ex vivo* to the subject. The claims do not preclude that the subject experiences a cell-mediated immune response against an antigen (e.g., viral antigen). Nor do the claims recite that one or more of a memory B cell and the plasma cell *induces* an immune response. Rather, the claims recite that the addition of the memory B cell and plasma cell *enhances* (i.e., improves) an immune response in a subject.

Viruses can be extracellular in the course of infection. Therefore, viral antigens can be extracellular antigens against which an immune response in the form of antibodies (e.g., against antigens of the viral envelope) would be beneficial. Thus, the administration of one or more of a memory B cell and the plasma cell can serve to *enhance* an immune response (e.g., a cellular-mediated immune response against a viral antigen).

As discussed previously, there is no requirement for working examples in the specification for an enabling specification. The specification discloses that a population of cells (e.g., B cell progenitors) that have been isolated from a subject can be contacted with IL-21 polypeptide or variant thereof, which results in the differentiation of the B cells into plasma cells and/or memory cells, which are then isolated (see, e.g., page 34, line 18, through page 35, line 3; and Examples 3-5). Furthermore, the specification discloses the administration of the isolated memory B cells and plasma cells to the subject to *enhance* an immune response (see, e.g., page 34, line 18, through page 35, line 3). Since antibody production (e.g., by plasma cells) is an essential element of the immune response, one of ordinary skill in the art would recognize that the inventive methods would be effective in *enhancing* an immune response in a subject.

Claims 18, 20, 34, and 35 recite a method for treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells by administering at least one of the memory B cell and plasma cell to the subject. As described above, the claims do not preclude that the subject experiences a cell-mediated immune

response against an antigen (e.g., viral antigen). Rather, the claims recite that a deficiency of at least one of memory B cells and plasma cells is remedied by specifically administering that which is deficient (i.e., at least one of memory B cells and plasma cells).

The Office also contends that the claims are not enabled for the genus of IL-21 agonists. As discussed above, the pending claims are directed to methods employing the IL-21 polypeptide of SEQ ID NO: 1 or a variant thereof that retains the ability to bind to the IL-21 receptor and produce the same physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor. The specification describes variants for use in the invention at, for example, page 31, lines 1-26, and cites to U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retaining the essential properties thereof. Ebner et al. discloses conserved regions of IL-21 polypeptide, such that one of ordinary skill in the art would have recognized regions of IL-21 polypeptide that should not be mutated in an IL-21 variant.

Additionally, assays to determine suitable IL-21 variants are described in the specification or known in the art. For example, the claims require that the IL-21 variant produces the same physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor. The specification describes that the IL-21 polypeptide activates the JAK/STAT signaling pathway (see, e.g., page 8, line 30, through page 9, line 5), induces differentiation of B cells and B cell progenitors into memory B cells and/or plasma cells (see, e.g., page 9, lines 6-20), induces expression of mRNA for Blimp-1 and Bcl-6 (see, e.g., page 53, lines 27-29), and inhibits expression of Pax5 mRNA (see, e.g., page 53, lines 27-30). Assays to determine if an IL-21 variant produces the above-described effects (e.g., real-time PCR) are known in the art and are described in the specification at, for instance, page 41, line 19, through page 44, line 16; and Examples 3-5.

Accordingly, based on the teachings in the specification and what was known in the art, one of ordinary skill in the art would have recognized how to perform the inventive methods without undue experimentation and with an expectation of success.

Discussion of the Objection to the Claims

The Office notes that there are two claims numbered 32 and 33 and requires correction. The second claims 32 and 33 have been renumbered to claims 34 and 35, respectively.

Applicants request that the objection to the claims be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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